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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/534,487 03/24/00 REID

L 114231.119

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HM22/0620

EXAMINER

WOITACH, J

ART UNIT

PAPER NUMBER

1632

3

DATE MAILED:

06/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/534,487

Applicant(s)
Reid, L.M. et al.

Examiner
Joseph Weitach

Group Art Unit
1632

☐ Responsive to communication(s) filed on _____.

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-20 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-20 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Art Unit: 1632

DETAILED ACTION

Applicants pre-amendment filed March 24, 2000, Paper No. 2, has been entered. Claims 1-20 are pending and are under current examination.

This application is a continuation of 09/115,920, which has been allowed, which is a continuation of 08/751,546, now Patent No. 5,789,246, which is a divisional of application 8/165,696, now patent 5,576,207, which is a continuation 7/741,128, now abandoned.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 2-4, 8-10, 11-13, 14 and 15 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-8 of prior U.S. Patent No. 5,789,246. This is a double patenting rejection.

Art Unit: 1632

Claim 2 of the present application, which is dependent on claim 1, is exactly the same in wording and scope as claim 1 of patent 5,789,246. Claims 1 and 2 recite all the limitations present in claim 1 of the patent. Further, claims 3, 4 and 8-10 of the present application are duplicates of claims 3-7 of patent 5,789,246, reciting further limitations drawn to claim 1. Claim 14 of the present application is a duplicate of claim 2 found in patent 5,789,246. Claims 10-13 separately contain only some of the limitations of claim 14, together, recite all the limitations of claim 14 and are essentially the same as claim 14. Further, claim 15 of the present application which recites a further limitation of claim 14 is an exact duplicate of claim 8, which further limits claim 2, of patent 5,789,246.

Claims 1, 6, 7, 11-16, 19 and 20 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-9, 17 of copending Application No. 09/115,920. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 1-18 of application 09/115,920 have been allowed, March 10, 2000. Claim 1 of the present application and claim 1 of application 09/115,920 are duplicates of each other. Claims 6, 7, 11-16, 19 and 20 recite further limitations to claim 1 of the present application and are exact duplicates of claims 2-9, 17 of application 09/115,920.

Obvious Type Double Patenting

Art Unit: 1632

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17 and 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 5,789,246. Although the conflicting claims are not identical, they are not patentably distinct from each other because each recite a composition of genetically engineered hepatocyte precursor cells.

Claim 17 recites genetically engineered hepatocyte precursor cells which are transferred to the same or different subject from where the cells were derived. Claim 18 recites that transfer comprises transplanting or grafting. Both claims are product claims drawn to a genetically engineered hepatocyte precursor cell and in this case the intended use for transferring the cells to a subject carries no patentable weight. Claim 17 is dependent on claim 16 which is dependent on claim 11 which have been both rejected for Provisional Double Patenting over claim 4 of application 09/115,920, and claim 11 has also been rejected for Statutory Double Patenting over claim 2 of patent 5,789,246, *supra*. Because claims 17 and 18 do not further limit claims 16 or

Art Unit: 1632

11, and only state an intended use for the genetically engineered hepatocyte, the product claims 17 and 18 are therefore obvious over claim 4 of application 09/115,920, and claim 2 of patent 5,789,246.

Claim 5 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 5,789,246 and claims 1 and 3 of U.S. Patent No. 5,576,207. Although the conflicting claims are not identical, they are not patentably distinct from each other because each recite a composition of genetically engineered hepatocyte precursor cells cultured on collagen alone or in combination of an extracellular matrix.

Claim 5 of the present application recites a composition comprising a cell culture wherein the collagen is used alone or in combination with proteoglycans, or tissue extracts enriched in extracellular matrix materials. Claims 1 and 3 of U.S. Patent No. 5,789,246 recites a composition of cells derived *in a* serum free culture medium, extracellular matrix and liver stromal cells (emphasis added for correction made in application but not in the published patent). The culturing conditions which makes-up the composition recited in claim 1 comprises any extracellular matrix, and claim 3 states that specific components of the extracellular matrix can be added in any combination thereof. Collagen, fibronectin, laminin and proteoglycans are all compounds which are defined as components of the extracellular matrix. Therefore, claims 1 and 3 recite a composition which encompasses any specific extracellular matrix in any number of

Art Unit: 1632

number of combinations. Claim 5 of the instant application recites a composition which clearly encompasses the composition of claims 1 and 3 of patent 5,789,246, because claim 5 simply restates that the extracellular matrix can be any combination of components. Further, the recitation of a composition of "tissue extracts enriched in extracellular matrix" encompasses unknown combinations of extracellular matrix and clearly reads on the broad undefined condition in claim 1. So in comparing the limitations of the claims, the vagueness and variation of the extracellular compounds recited in patent 5,789,246 encompasses any limitation recited in claim 5 of the instant application. While claims 1 and 3 do not specifically recite that the culture should include proteoglycans or that the extracellular matrix is derived from tissue extracts in the claims, optimization of culturing conditions is generally accepted as routine in the art, and in this case, proteoglycans are one type of many types of extracellular matrix used in culturing cells, therefore claim 5 does not further limit the scope of claims 1 and 3 and as such, are obvious over each other.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transferring the genetically altered hepatocyte to the same

Art Unit: 1632

subject from which they are derived, does not reasonably provide enablement for transferring the genetically altered hepatocyte to a different subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue". The specification is not enabling for the claimed invention because the specification does not provide sufficient guidance, evidence or exemplification so that an artisan of skill would have been able to make and use the invention as claimed invention without undue experimentation.

In the instant case, the claimed composition encompasses a method wherein cells from one organism are transferred to a second different organism, essentially performing xenotransplantation. While transplantation of tissues from one individual to another who demonstrates a tolerance due to histocompatibility is generally accepted in the art, the successful

Art Unit: 1632

transfer of cells and tissues from one species to another continues to pose several technical difficulties due to immunological barriers. The specification is not enabling for the claimed invention because the specification fails to provide any guidance, working example or evidence as to how an artisan of skill would have practiced said transfer without undue experimentation.

At the time of the invention Ryan highlighted the major obstacle to xenotransplantation as hyperacute rejection (HAR), which leads rapidly to irreversible organ damage and xenograft loss. At the time no agents in clinical practice could prevent HAR (page 967; first paragraph). Two factors; 1) the presence of natural antibodies to the xenograft and 2) complement, via both classical and alternative pathways are the main forms of HAR. Ryan summarized that ‘if xenotransplantation is to become a clinical reality, a clinically relevant means of inhibiting complement activation is required’, and “[o]nce complement-mediated HAR has been inhibited, the full spectrum of cellular and antibody-mediated inflammatory and immune responses characteristic of acute and chronic rejection” (page 968; final paragraph). The specification is silent with respect to examples or guidance on how one would overcome these problems generally encountered in xenotransplantation.

With respect to transplantation of hepatocytes, currently, these obstacles have still not been overcome. Porter *et al.* in a summary of the work of Ringden *et al.* report that in an attempt to increase graft vs. tumor effect, for treatment of hepatocellular carcinoma, and reduce graft vs. host disease, bone marrow transplantation was done to create mixed chimerism across HLA barriers (page 2004; middle of first column). However, “initial engraftment was transient” and

Art Unit: 1632

“intensive immunosuppressive therapy was ineffective in reversing ‘rejection’” (following line). While the ideal outcome is the generation of mixed chimerism allowing autologous immune reconstruction to induce tolerance to transplantation of non-self cells or tissues, the “conditions required to permit sustained mixed chimerism will need to be elucidated” (page 2004; middle of column two).

A more recent advance in xenotransplantation is the use of genetically modified cells and particular tissues from pigs. As in other allogenic and xenogenic transplantations, HAR lead to the destruction of transplanted pig tissue when no other steps are taken. Cozzi *et al.* teach that one way to prevent HAR is through the use of regulators of complement activation (RCAs). It is hypothesized that cells from donors which express RCAs could prevent lysis of the cells subsequent to human compliment activation (page 964; top of middle column and figure 1). While perfused hDAF transgenic organs were resistant to human compliment activation when perfused with human blood, Cozzi *et al.* it si still necessary to demonstrate that such organs had become resistant when transplanted (page 965; column one). Further, while genetic manipulation will overcome compliment-mediated component of rejection, anti-species antibody remains a potential problem in its ability to cause endothelial activation or lysis (page 965; middle column).

In summary, there is a need for alternative sources of cells and tissues for transplantation, however, there are many barriers to transplantation, in particular to xenotransplantations, as outlined above. The specification does not provide any guidance nor example as to how an artisan would have dealt with these limitations or overcome the barriers which exist.

Art Unit: 1632

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 5 is unclear because collagen and proteoglycans are extracellular matrix materials which would be encompassed in the recitation in claim 2 of "comprising extracellular matrix". It is not clear that by the addition of these to the composition in claim 5, that it was meant that they were not included in the extracellular matrix material previously recited, or that they were present and the claim means to augment the composition with extra amounts of these materials.

Claims 17 and 18 are unclear because they recite method steps in a product claim. Claim 17 is drawn a genetically modified hepatocyte precursor cells which are derived by genetically modifying hepatocyte precursor cells *ex vivo* as recited in claim 16 and claim 11. The intended use for a product claim, in this case the transferring of the claimed cells from one subject to

Art Unit: 1632

another does not carry any patentable weight. It is not clear what or how the steps recited in the claims affect the claimed cells that make them different or distinct from those in claims 11 and 16.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Jasmine Chambers, can be reached on (703) 308-2035. The fax number for group 1600 is 1(703)308-4242.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

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